Remarks/arguments

Claims 1, 4 - 39 are presently in the case. Entry of this amendment is respectfully requested. No new matter is added by the amendment, because the amended application is fully supported by the application as filed. More specifically, the amended Claims 1 and 27 are supported by the disclosures in the specification on, for example, page 17, line 26 - page 18, line 6 and page 13, lines 13 - 20. New claims 37 - 39 have been added. Support for claim 37 can be found in the specification at, for example, page 23, lines 9 - 22 and in claim 5. Support for claim 38 can be found in the specification at, for example, page 11, line 3. Support for claim 39 can be found in the specification at, for example, page 11, lines 1 - 25 and page 36, lines 13 - 25.

Telephonic Interview

Applicants would like to thank the Examiner for the courtesies he extended during the telephonic interview on August 31, 2004. The Examiner indicated that he would be completing an Interview Summary and Applicants request that the Examiner provide them with a copy of the Summary.

Claim Rejections - 35 USC §112

1. Claims 1 and 4- 36 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically it is allegedly unclear what applicant means by "said lipid and co lipid form preexisting lipid domains wherein the co-lipids are clustered in discrete domains". Similarly Claim 27 recites "capable of forming preexisting lipid domains

wherein the co lipids are clustered in discrete domains" The Examiner indicates that how this is accomplished should be recited fully in the method claim 27.

Applicants have amended claims 1 and 27 to clarify the claim language by deleting the phrase "capable of forming preexisting lipid domains". Applicants believe that the claims as amended are now clear and withdrawal of this rejection is respectfully requested.

2. Claims 32 and 33 stand rejected on the basis that there is no antecedent basis for the term "liposome" in Claim 10, from which Claim 32 depends.

Applicants have amended claims 32 and 33 to recite a liposome delivery system. Withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 USC §102(b)

Claims 1, 4, 9-11, 16-17, 19 and 23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lamparski (Biochemistry, vol. 31., 1992). The Examiner alleges that Lamparski discloses liposomes containing a phospholipid and a polymerizable colipid and that the polymerizable lipid upon polymerization with UV radiation polymerizes and destabilizes the liposomes thereby leaking the contents.

Claim 1 has been amended to recite an ionizing radiation sensitive liposome delivery system, comprising a stable liposome-forming lipid and an ionizing radiation polymerizable colipid, wherein after administration to a patient the colipids are clustered in discrete domains.

The subject matter of the amended Claim 1 and Lamparski are different in many aspects.

Applicants Invention

Generally, in order for liposomes to reach the target site in the patient without significant loss of their contents, passive leakage of the contents must be slow relative to the time required

for liposomes to circulate and escape the vasculature. It would be desirable to stimulate enhanced release of the encapsulated agent from the liposomes once the liposomes are at the target site or tumor site in a patient.

Applicants have discovered that by selecting certain lipids and ionizing radiation polymerizable colipids, Applicants can generate a liposome in which the colipids in the liposome are clustered in discrete domains when the unpolymerized liposome is administered to a patient. Applicants have also shown that if the colipids are clustered in discrete domains at the time of ionizing radiation, the radiation has a greater effect in destabilizing the liposome, thereby releasing more of the agent present within the liposome. Accordingly, it is possible to achieve enhanced release of the encapsulated agent from the liposomes once the liposomes are at the target site. Use of ionizing radiation is beneficial, because it can penetrate the patients body and be directed to the site where release of the agent is desired.

Lamparski et al.

The Examiner states that the distribution of the lipids (whether random or discrete domain) is temperature dependent, therefore the distribution of lipids in the Lamparski preparations would be as "discrete domains" below the room temperature.

Applicants have amended Claim 1 to recite that the colipids in the liposomes form discrete domains when the liposomes are in a patient.

MPEP §2131 provides, "'A claim is anticipated only if *each* and *every* element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). A showing that the prior art reference lack[ed] the characteristics of the

claimed invention would in fact negate the assertion that the claimed invention was described in the prior art. *In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)*

Applicants respectfully point out that the global transition temperature of the liposomes disclosed in Lamparski are substantially below the room temperature. Accordingly, the temperature at which the liposomes disclosed in Lamparski would potentially form discrete domains would be at a temperature which is below room temperature. The Declaration of Dr. O'Brien[1] states that in Lamparski the liposomes were composed of DOPE or DOPC in either a 2:1 or 3:1 molar ratio with bis-SorbPC (para. 6).

> "The main phase transition temperature of DOPC is -20°C. The main phase transition temperature of DOPE is -10°C. The main phase transition temperature of the bis-SorbPC used in the Lamparski study is 27°C. Therefore, the liposomes prepared and studied in Lamparski were designed to form fluid phase liposomes at room temperature and above. Furthermore, at 3:1 molar ratio with bis-SorbPC, the global transition temperature would have been substantially below the room temperature. These conditions favor random mixing of the lipids and bis-SorbPC where polymerizable colipids are randomly distributed throughout the liposomal membrane."

The liposomes disclosed in Lamparski would not form discrete domains in a patient because body temperature (37°C) is above the temperature at which the liposomes of Lamparski form discrete domains. Accordingly, the liposomes taught by Lamparski do not anticipate the claimed invention. In this case, there is no disclosure, either inherent or explicit, in Lamparski which would indicate *the colipids are clustered in discrete domains after the liposome is administered to a patient.* Accordingly, Lamparski et al. does not disclose *each* and *every* element as set forth in the claims, either expressly or inherently.

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1 The Declaration of Dr. O'Brien was previously filed in this application on June 28, 2002.

During the interview, the Examiner stated that the limitation "wherein the colipids are clustered in discrete domains after administration to a patient" is a statement of intended use and not a limitation on the claimed liposome delivery system. Applicant respectfully disagrees. MPEP Section 2173.05(g) describes a functional limitation as a limitation that defines something by what it does, rather than by what it is. This Section states that "There is nothing inherently wrong with defining some part of an invention in functional terms." In *In re Barr, 444 F.2d 588, 170 U.S.P.Q. 33 (CCPA 1971),* the board held that the limitation "incapable of forming a dye with said oxidizing developing agent" used to define a radical was perfectly acceptable. Similarly, in the present case, Applicant is not attempting to claim that the colipids are administered to a patient. Rather, Applicant is claiming the limitation that upon administration the colipids are clustered in discrete domains. Thus, as explicitly recognized by the MPEP as being acceptable, Applicant is claiming the colipids in functional terms, or by what it does.

The amendment to Claim 1, therefore, is believed to overcome the rejection under 35 USC 102(b) and the Examiner is respectfully requested to reconsider and withdraw the rejection.

Claim Rejections - 35 USC §103(a)

1. Claims 1, 4-5, 9-11, and 16-31, 33 and 36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lamparski in view of either Heldebrant (U.S. Patent No. 5,061,484) or Charych (U.S. Patent No. 6,180,135) in further combination with Hallahan (U.S. Patent No. 6,159,443). The Examiner alleges it would be obvious to one of ordinary skill in the art to use the liposomes of Lamparski for the delivery of the diagnostic or therapeutic agents with a reasonable expectation of success since Lamparski provides guidance as to how to prepare the liposomes and suggests their use. Lamparski teaches only the application of ultraviolet radiation

as the source. However, in the absence of a showing of criticality, it is allegedly deemed obvious to use any form of ionization as long as they polymerize the lipid. The use of X-rays as the ionizing radiation with the liposomes of Lamparski would have been obvious to one of ordinary skill in the art since X-rays are not only another form of ionizing radiation to polymerize the liposomal lipids as shown by Heldebrant or Charych, but also provide an improved method of delivery when combined with delivery vehicles such as the liposomes shown by Hallahan. Hallahan discloses administering a therapeutic agent or diagnostic agent in a delivery vehicle (liposome). The liposome also contain antibodies attached to them.

Applicants respectfully disagree.

For the claimed subject matter to be obvious in view of a combination of prior art references, the prior art must suggest the combination to one of ordinary skill in the art and reveal that one of such skill would have a reasonable expectation of success in carrying out the invention. *In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).*

Lamparski has already been discussed in the rejection under 35 U.S.C. 102. First, Lamparski does not teach that the colipids should be clustered in discrete domains at the time of polymerization in order to further destabilize the liposomes. Secondly, as the Examiner noted, Lamparski does not teach or suggest the use of ionizing radiation to destabilize the liposome.

Charych teaches polymerized polymeric assemblies (ie. liposomes) which change from a blue to red color when exposed to an analyte as a diagnostic product. In Charych, diacetylenes are combined into a liposome and the liposome is polymerized with a UV lamp in vitro. Charych does teach that X-rays are another polymerization means. Charych does not teach the administration of his liposomes to patients. Charych does not teach or suggest the benefit of having the colipid form discrete domains before polymerization. Charych does not teach or

suggest administration of unpolymerized liposomes to a patient. Charych does not teach or suggest selecting a colipid and lipid such that the colipid would form discrete domains in the unpolymerized liposome when administered to a patient.

Heldebrant teaches a stable perfluorochemical emulsion which comprises perfluorochemical particles in stabilized vesicles. The stabilized vesicles comprise a biocompatible polymer formed by coating the perfluorochemical particles with one or more phospholipid monomers and polymerizing the monomers. The stabilized/polymerized liposome is then administered to a patient. The purpose of the polymerization is to generate more stable emulsions which (1) can withstand higher and longer sterilization temperatures and times, (2) possess greater stability after sterilization with permits longer storage times; and (3) have longer circulating in vivo half-lives. Heldebrant does not teach or suggest selecting a colipid and lipid such that the colipid would form discrete domains in the liposome which administered to a patient. Heldebrant does not teach or suggest administering an unpolymerized liposome to a patient. Heldebrant does not teach or suggest releasing the perfluorochemical from the liposome. In fact, Heldebrant specifically teaches away from the claimed invention by indicating that the liposome should be composed of only polymerizable colipids and be completely polymerized before administration to a patient to ensure stability of the polymerized liposome in the patient and to prevent the release of the perfluorochemical (Col. 6, lines 29 - 40).

Hallahan teaches a targeting technique of delivering an active agent to a target tissue, particularly neoplastic tissue. Hallahan teaches the use of ionizing radiation targeted at tumor sites to induce platelet aggregation. Hallahan teaches the attachment of a delivery vehicles to platelets to increase the targeting of the delivery vehicles. One of many different targeting vehicles mentioned by Hallahan are liposomes. The already polymerized liposomes taught by

Hallahan are conjugated to the platelets and carried by the platelets to the site of ionizing radiation after the administration of the ionizing radiation. Hallahan does not teach or suggest the administration of a ionizing radiation sensitive liposome to a patient. Hallahan does not teach or suggest the use of X-rays to polymerize any type of unpolymerized liposome in the patient. Accordingly, Hallahan does not teach or suggest a liposome comprising a lipid and an ionizing radiation polymerizable colipid which forms discrete domains when administered to a patient.

Accordingly, none of the references, either alone or in combination, teach or suggest a liposome delivery system comprising a lipid and ionizing radiation polymerizable colipid which forms discrete domains when administered to a patient. First, none of the references teach or suggest, either alone or in combination, the selection of lipids and colipids to form a unpolymerized liposome delivery system which forms discrete domains after administration to a patient. Second, none of the references teach or suggest that ionizing radiation energies that are much higher than UV would cause the clustered colipids to polymerize thereby releasing the contents from the liposome. UV radiation excites an electron. Excitation of electrons results in a higher likelihood of polymerization of the polymerizable colipid. On the other hand , ionizing radiation photons in their interaction with matter can result in the complete displacement of an electron with a reduced likelihood of polymerization. Accordingly, it is not obvious that the claimed liposome delivery system would comprise an ionizing radiation sensitive colipid. Absent such a teaching the claimed invention is not obvious and withdrawal of this rejection is respectfully requested.

2. Claims 5-8 and 12-15, and 34-35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski in view of either Heldebrant ('484 patent"), Charych (the '135 patent") in further combination with Hallahan ("the '443 patent") and further in view of Woodle (BB 1992). The Examiner indicates that what is lacking in Lamparski and the other references already discussed are the teaching of the inclusion of PEG in the liposomal compositions.

This rejection is also respectfully traversed. Claim 5 depends from Claim 1. For the reasons set forth above, Claim 1 is not obvious.

The teachings of Lamparski, the '484 patent, the '135 patent and the '443 patent have already been discussed.

Woodle does teach the use of pegylated lipids in liposomes. Woodle does not teach the selection of lipids and ionizing radiation polymerizable colipids such that the colipids in the unpolymerized liposome form discrete domains. Absent such a teaching, Woodle does not cure the deficiencies of the other references and the claims are not rendered obvious.

Consequently, there exists no intrinsic basis or extrinsic justification for the proposed combination of Lamparski with Heldebrant, Charych, Hallahan and Woodle and *prima facie* obviousness has not been established. Applicants respectfully traverse the rejection of those claims.

Conclusion

Entry of the amendment, and reexamination, reconsideration, and early allowance of claims 1 and 4-39 are therefore respectfully requested. Applicants note that the amendments herein do not indicate Applicants' agreement to the propriety of the rejections, and Applicants reserve the right to pursue claims such as those presented previously in a related application.

Please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641.

Respectfully submitted,

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